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ART UNIT	PAPER NUMBER
1642	18

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/068,377	LASKY ET AL.	
	Examiner	Art Unit	
	Stephen L. Rawlings, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Peri d for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 September 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-21 and 23* is/are pending in the application.

4a) Of the above claim(s) *1-14 and 19-21* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *15-18 and 23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-21 and 23* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on September 24, 2001 (Paper No. 26) has been entered.

2. The amendment filed on July 9, 2001 in Paper No. 22 is acknowledged; although, it is noted that Applicant did not explicitly request that the amendment, which was filed After-Final, be entered. Nevertheless, in Paper No. 27, Applicant states the following:

> After entry of the Amendment After Final and Response submitted by Applicants on July 6, 2001, claims 15-18 and 23 will be pending (page 1, paragraph 1).

Consequently, it has been presumed that Applicants intended to request that the amendment be entered. Accordingly, claim 15 is amended, claim 22 is canceled, and claim 23 is added.

In response to the Office Action, Applicant is requested to affirm the apparent, albeit inexplicit request to have the amendment filed on July 9, 2001 in Paper No. 22 entered.

3. The amendment filed on September 24, 2001 in Paper No. 27 is acknowledged and has been entered. Claim 15 is amended.

4. Claims 1-21 and 23 are pending in the application. Claims 1-14 and 19-21 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a non-elected invention, there being no allowable generic or linking claim. Applicants timely traversed the restriction (election) requirement in Paper No. 12.

5. Claims 15-18 and 23 are currently under prosecution.

Priority

6. This application has fulfilled the requirements of 35 USC §§ 119(e) and 120 to receive benefit of the earlier filing dates of domestic applications 60/104,589, 08/938,830, and PCT/US98/01774.

Oath/Declaration

7. Receipt of the new declaration, which is in compliance with 37 CFR 1.67(a), is acknowledged and has been entered.

Specification

8. Receipt of the abstract of the disclosure as required by 37 CFR 1.72(b) is acknowledged and has been entered.

In addition, it is noted that the specification has been to amended to properly claim benefit of the earlier filed applications in accordance with 37 CFR 1.78.

Claim Objections

9. Claims 15 and 23 are objected to because of the following informalities:

Claims 15 and 23 refer to a figure; however, because the figure will not be published, the referral to the figure will cause confusion. It is noted that the claims also refer to a particular sequence identification number, which will be published. A referral to this number is both appropriate and sufficient. Therefore, Applicants are encouraged to delete the referral to the figure in claims 15 and 23.

Claim Rejections - 35 USC § 112

10. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make

and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. Claim 23 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claim 23 is drawn to an assay for identifying a cell membrane permeable antagonist or agonist antibody of a PST phosphatase interacting protein (PSTPIP), wherein said assay comprises contacting the PSTPIP with a candidate antibody and monitoring the ability of the antibody to stimulate or inhibit the polymerization of actin monomers induced by over-expression of the PSTPIP within a cell.

The teachings of the specification cannot be extrapolated to the enablement of the invention commensurate in scope with the claims because ordinarily a cell membrane is impermeable to a molecule the size of an antibody and the specification does not disclose a method for producing an antibody that is cell membrane permeable. The claimed assay is not exemplified in the specification and otherwise there is insufficient guidance disclosed therein to enable one skilled in the art to practice the invention. Accordingly, one of skill in the art would not be able to practice the claimed invention with a reasonable expectation of success without first performing extensive and undue experimentation. First of all, in order to practice the claimed invention, the artisan would have to develop a method for producing an antibody able to permeate the membrane of a cell. Clearly undue experimentation would be required to do so, since a method for producing a cell membrane permeable antibody is conventional or well known in the art. Secondly, one would have to determine if after the necessary modification the antibody would retain specific binding affinity for the PSTPIP within the cell. Only then would one be able to practice the claimed assay to identify an antibody that either stimulates or inhibits the polymerization of actin monomers induced by over-expression of the PSTPIP within a cell.

In view of the above, the specification fails to meet the enablement requirement of 35 USC § 112, first paragraph.

12. Claims 15-18 and 23 are rejected under 35 USC § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, has possession of the claimed invention.

Claims 15-18 are drawn to an antibody that binds specifically to a PST phosphatase interacting protein (PSTPIP), wherein said PSTPIP comprises the amino acid sequence of SEQ ID NO: 1, which is encoded by the polynucleotide sequence set forth in SEQ ID NO: 2, or alternatively wherein said PSTPIP comprises an amino acid sequence encoded by a nucleic acid molecule that hybridizes under specifically claimed stringent hybridization conditions to the complement of residues 682 to 1926 of SEQ ID NO: 2 wherein said PSTPIP has the ability to stimulate actin polymerization and the ability to bind to a protein tyrosine phosphatase that (a) possesses a non-catalytic domain comprising a region rich in proline, serine, and threonine residues and a C-terminal 20 amino acid segment that is rich in proline residues and (b) defines at least one SH3 binding domain. Claim 17 is drawn specifically to the antibody of claim 15 that is a monoclonal antibody. Claim 18 is drawn to a hybridoma that produces the antibody of claim 15, which is necessarily a monoclonal antibody. Therefore, claims 15-18 encompass a genus of antibodies, which includes both polyclonal and monoclonal antibodies that bind specifically to a genus of PST phosphatase interacting proteins (PSTPIPs), wherein said genus of PSTPIPs includes but is not limited to the mouse PSTPIP consisting of the amino acid sequence of SEQ ID NO: 1. Claim 23 is drawn to an assay for identifying a cell membrane permeable antagonist or agonist antibody of a PSTPIP and therefore is drawn to a method comprising the use of at least a subgenus of the claimed genus of antibodies.

However, the specification describes only one species of the broad genus of PSTPIP to which the claims refer. More particularly, the specification discloses the amino acid sequence of a mouse PSTPIP that consists of the amino acid sequence of SEQ ID NO: 1, which is encoded by the polynucleotide sequence of SEQ ID NO: 2. While the specification also discloses the polynucleotide sequence of a human nucleic

acid molecule, i.e., SEQ ID NO: 29, which presumably hybridizes under the stringent conditions set forth in the claims to the complement of residues 682 to 1926 of SEQ ID NO: 2, the specification does not disclose that the protein encoded by SEQ ID NO: 29 has the ability to stimulate actin polymerization and to bind to a protein tyrosine phosphatase that (a) possesses a non-catalytic domain comprising a region rich in proline, serine, and threonine residues and a C-terminal 20 amino acid segment that is rich in proline residues and (b) defines at least one SH3 binding domain.

The Examiner acknowledges that the claimed subject matter of the parent application, which issued as US Patent No. 6,111,073-A, also encompasses the genus of PSTPIP molecules to which the claimed antibodies of the instant application must bind; nevertheless, for the reason set forth in the paragraph above, it is not clear from the disclosure that Applicants describe more than one species of PSTPIP. With particular regard to the instant application, then, it is noted that the specification perhaps only includes an adequate description of a single species of the genus of PSTPIP molecules, but would necessarily need to provide a written description of a more reasonable number of the members of the genus to convey to one skilled in the art that at the time the application was filed, Applicants has possession of a reasonable number of the members of the claimed genus of antibodies that bind specifically to the various and different members of the genus of PSTPIP molecules. Obviously, if Applicants do not provide sufficient disclosure to demonstrate possession of a reasonable number of PSTPIP molecules, it would not be possible to provide a sufficient disclosure demonstrating possession of a reasonable number of the claimed antibodies, because without the protein, one could not have an antibody that specifically binds the protein.

The written description apparently only includes a disclosure of a rabbit polyclonal antiserum raised against a fusion protein comprising SEQ ID NO: 2. Therefore, the specification fails to describe a monoclonal antibody that binds specifically to the protein comprising SEQ ID NO: 2. Furthermore, the specification fails to describe any other polyclonal or monoclonal antibody that binds specifically to any other species of PSTPIP. Consequently, there appears to be no factual evidence in the

specification that would serve to reasonably convey to one skilled in the art that Applicants had possession of the claimed invention at the time the application was filed.

Of course, if Applicants had possession of a reasonable number of the members of the genus of PSTPIP molecules to which the claims refer, it would be conventional and routine to produce antibodies that bind specifically to those molecules; however, Applicant is reminded that regardless of the simplicity of producing an antibody to a protein, evidence of conception alone is not a sufficient indication to reasonably convey to one skilled in the art that Applicants had reduced to the invention to practice at the time the application was filed.

Vas-Cath Inc. V. Mahurkar, 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*" (page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed" (page 1116). Furthermore, the court's decision makes clear that the written description provision of 35 USC 112 is severable from its enablement provision (page 115).

Noticeably, also, the disclosure does not appear to include a description of any one species of the subgenus of the claimed genus of antibodies that are able to bind PSTPIP and either augment or hamper the activity of PSTPIP upon binding. In other words, the claimed assay is not exemplified in the specification and the characteristics of a cell permeable antagonist or agonist antibody, which may have been identified in practicing the invention, are not disclosed therein. In fact, the most comprehensive description of the subject matter that Applicants regard as the invention may be in the claims, wherein it is disclosed that the members of the claimed genus of antibodies bind specifically to a polypeptide comprising the amino acid sequence of SEQ ID NO: 1 or alternatively, to a polypeptide comprising an amino acid sequence encoded by a nucleic acid molecule that hybridizes under specifically claimed stringent hybridization conditions to the complement of residues 682 to 1926 of SEQ ID NO: 2 wherein said PSTPIP has the ability to stimulate actin polymerization and the ability to bind to a

protein tyrosine phosphatase that (a) possesses a non-catalytic domain comprising a region rich in proline, serine, and threonine residues and a C-terminal 20 amino acid segment that is rich in proline residues and (b) defines at least one SH3 binding domain. However, recitations in the claims alone do not constitute a sufficient description of the genus of antibodies to which the claims refer to enable one skilled in the art to immediately visualize or recognize the identity of the members of the genus. Adequate written description requires more than a mere statement that it is part of the invention and a reference to a potential method of isolating it. The invention itself is required. See *Fiers v. Revel*, 25 USPQ 2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Lts.*, 18 USPQ2d 1016. Therefore, with regard to the claimed subject matter of claim 23, it again appears that a reduction to practice had not occurred at the time the application was filed.

The Federal Circuit recently clarified the application of the written description requirement to inventions in the field of biotechnology. See *University of California v. Eli Lilly and Co.*, 119 F.3d 1559, 1568, 43, USPQ2d 1398, 1406 (Fed. Cir. 1997). Consideration of the court's findings suggests that a generic statement of effect is not deemed an adequate written description because it does not distinguish the genus from others, except by function. Such a generic statement fails to define a species of antibody that falls within its definition. Therefore, defining the genus of PSTPIP molecules to which the claims refers as having the ability to stimulate actin polymerization and the ability to bind to a protein tyrosine phosphatase with particular structural characteristics does not suffice to define the genus, because it is only an indication of what the protein must do, rather than what the protein is. The court's findings suggest that an adequate description of a genus may be achieved by means of a recitation of a representative number of members of the genus or a recitation of specific structural features common to members of the genus, which constitute a substantial portion of the genus. However, again, it is noted that the specification only identifies a single species of the genus of PSTPIPs, which has been demonstrated to meet the limitations of the claims, and therefore it fails to identify a representative number of members of the genus of the molecules to which the claims refer. Because

the genus of PSTPIP molecules is not adequately described, it follows that the claimed genus of antibodies that bind specifically to members of the genus of PSTPIP molecules cannot be adequately described. Even so, it is noted for example, that the specification does not include a description of a structural feature, such as the complementarity determining regions that is common to the members of the claimed genus of antibodies. Certainly, since one skilled in the art would not be able to distinguish a member of the genus of PSTPIP molecules to which the claims refer, one would also not be able to distinguish a member of the claimed genus of antibodies from those that are not claimed. Because the claimed genus of antibodies is not adequately described, it also follows that the claimed genus of assays that use the different members of the genus of antibodies cannot be adequately described. Consequently, the disclosure fails to meet the written description requirements of 35 USC § 112, first paragraph.

13. Claims 15-18 and 23 are rejected under 35 USC § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, has possession of the claimed invention.

With regard to claims 15 and 23, there appears to be inadequate antecedent basis for the limitation "the complement of nucleic acid residues 682 to 1926 of SEQ ID NO: 2" in the specification. Accordingly, this limitation embodies new matter. While residues 682 to 1926 are intrinsic to the polynucleotide sequence of SEQ ID NO: 2, the specification does not disclose any import to be particularly associated with residues 682 to 1926 of SEQ ID NO: 2 or for that matter, any other fragment of the polynucleotide sequence. Applicant is reminded that it cannot be said that a subgenus is necessarily described by a genus encompassing it and a species upon which it reads. See *In re Smith*, 173 USPQ 679, 683 (CCPA 1972). With regard to claims 15 and 23, the specification fails to disclose the subgenus of antibodies that bind a polypeptide encoded by a nucleic acid molecule that hybridizes under stringent conditions to the complement of residues 682 to 1926 of SEQ ID NO: 2, but which do not bind a polypeptide encoded by a nucleic acid molecule that hybridizes to the complement of

other portions of SEQ ID NO: 2; therefore, the specification fails to provide proper antecedent basis for the limitations of subject matter in the claims. Such a limitation recited in the present claims, which is not supported by disclosure in the specification, introduces new concepts and violates the written description requirement of 35 USC § 112, first paragraph.

Furthermore, it is noted that the recitation of "a polypeptide encoded by nucleic acid which hybridizes under stringent conditions to the complement of nucleic acid residues 682 to 1926 of SEQ ID NO: 2" appears to be a negative limitation since it excludes polypeptides encoded by nucleic acid molecules that hybridize under stringent conditions to the complement of other portions of SEQ ID NO: 2. Adding the expressed exclusion of certain elements implies permissible inclusion of all other elements not so expressly excluded. This clearly illustrates that such negative limitations, in fact, introduce new concepts. See *Ex parte Grasselli*, 231 USPQ 393 (BPAI 1983).

For the reason stated in the paragraphs above, there also does not appear to be proper antecedent basis for the recitation of the phrase "[a]n antibody that binds specifically to a PST phosphatase interacting protein (PSTPIP) sequence *within* a polypeptide" (italics added) in claim 15. The specification fails to disclose the subgenus of antibodies that bind specifically to any particular subsequence within a polypeptide comprising the amino acid sequence of the PSTPIP. While certainly the recitation of the phrase excludes antibodies that bind specifically to an amino acid sequence of the polypeptide, which is not part of the amino acid sequence of the PSTPIP, it cannot be ascertained which other antibodies that bind specifically to an amino acid sequence of the polypeptide are also excluded. In this regard it is appropriately noted that the specification incongruously defines the term "PST phosphatase interacting protein (PSTPIP)" as "a polypeptide which **comprises** the amino acid sequence of the PSTPIP polypeptide shown in Fig. 1A (SEQ ID NO:1)" (emphasis added) (page 7, lines 15-17). While it is difficult to envision which proteins Applicants would and would not consider PSTPIP polypeptides, since the according to the somewhat incongruous definition, it is fairly clear that Applicants intended the definition of PSTPIP to encompass fusion proteins comprising the conjugate of the amino acid sequence of a PSTPIP molecule

and the amino acid sequence of some undisclosed protein. Therefore, based upon the definition of "PSTPIP", the claims might reasonably be interpreted to encompass an antibody that binds to an amino acid sequence of a heterologous peptide, such as the FLAG epitope of a fusion protein also comprising the amino acid sequence of a protein having the ability to bind the specifically claimed protein tyrosine phosphatase and induce actin polymerization within a cell, but Applicants have argued that such antibodies are not regarded as the invention. For this reason, amending claim 15 to recite "[a]n antibody that binds specifically to a PST phosphatase interacting protein (PSTPIP) sequence within a polypeptide" appears to direct the claim to a subgenus of antibodies, which was not described by the original disclosure of the genus of antibodies that bind specifically to a PSTPIP polypeptide comprising the amino acid sequence of SEQ ID NO: 1. Again, Applicants are reminded that it cannot be said that a subgenus is necessarily described by a genus encompassing it and a species upon which it reads. See *In re Smith*, 173 USPQ 679, 683 (CCPA 1972). Furthermore, for this reason, it appears that the phrase "[a]n antibody that binds specifically to a PST phosphatase interacting protein (PSTPIP) sequence within a polypeptide" is a negative limitation since it is intended to exclude antibodies that do not bind specifically to an amino acid sequence of SEQ ID NO: 1 within the PSTPIP polypeptide. Once again, adding the expressed exclusion of certain elements implies permissible inclusion of all other elements not so expressly excluded. This clearly illustrates that such negative limitations, in fact, introduce new concepts. See *Ex parte Grasselli*, 231 USPQ 393 (BPAI 1983).

With regard to claim 23, there appears to be inadequate antecedent basis for the term "cell membrane permeable antagonist or agonist antibody" in the specification. Again, Applicant is reminded that it cannot be said that a subgenus is necessarily described by a genus encompassing it and a species upon which it reads. See *In re Smith*, 173 USPQ 679, 683 (CCPA 1972). Accordingly, the amendment of the claims to recite this term introduces new matter.

Furthermore, with regard to claim 23, although Applicants state that the necessary support for the phrases "to stimulate or inhibit the polymerization of actin

monomers induced by over-expression of the PSTPIP polypeptide within a cell" and "identifying an agonist if there is an increase in the level of actin polymerization and an antagonist if there is a decrease in the level of actin polymerization" can be found on page 8, lines 29-38 of the specification, support for these phrases is not explicit. Therefore, there appears to be inadequate antecedent basis in the specification for the recitation of these phrases in claim 23, which then would constitute introduction of new matter. It would be advisable for Applicants to amend claim 23 to recite the language used in the specification on page 8, lines 29-38, or else to explain how the disclosure implicitly provides sufficient antecedent basis to support the recitation of the phrases in the currently pending claim.

14. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

15. Claims 15-18 and 23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 15-18 are vague and indefinite because claim 15 recites the phrase "a PST phosphatase interacting protein (PSTPIP) polypeptide sequence within a polypeptide selected from the group consisting of (i) a polypeptide comprising the amino acid sequence of the PSTPIP polypeptide shown in Fig. 1A (SEQ ID NO: 1)". Recitation of the phrase renders the claim vague and indefinite because it cannot be ascertained to which subsequence within the amino acid sequence of the PSTPIP of SEQ ID NO: 2 the claim refers. Moreover, recitation of the phrase also renders the claim vague and indefinite because while the term "PST polypeptide interacting protein (PSTPIP) polypeptide sequence" is defined by the first member of the Markush group of the claim under (i) as the sequence set forth in SEQ ID NO: 1, the claims are clearly drawn to a genus of PSTPIP molecules, which apart from the PSTPIP of SEQ ID NO: 1, have amino acid sequences that are not disclosed and therefore upon consideration of breadth of scope encompassed by the second member of the Markush group of the

claim, the term "PST polypeptide interacting protein (PSTPIP) polypeptide sequence" is not adequately defined by the claim so as to be considered to particularly point out and distinctly claim the subject matter that Applicants regard as the invention. As stated in the rejection above, the subject matter of claim 15 is not adequately described to meet the written description requirement of 35 USC § 112, first paragraph. Thus, the specification provides insufficient disclosure to enable one of ordinary skill in the art to visualize and recognize the amino acid sequences of the PSTPIP molecules to which the claims refer. Therefore, it would not be obvious or apparent to which subsequence of a protein comprising the amino acid sequence of the PSTPIP the claims require the antibody to bind. Moreover, it is noted that the specification defines the term "PST phosphatase interacting protein (PSTPIP)" as "a polypeptide which **comprises** the amino acid sequence of the PSTPIP polypeptide shown in Fig. 1A (SEQ ID NO:1)" (emphasis added) (page 7, lines 15-17). According to the definition, then, even though it appears to be incongruous, a PSTPIP molecule may comprise an amino acid sequence of a protein other than the PSTPIP of SEQ ID NO: 1. In light of the incongruity of the definition, most certainly, it would not be obvious or apparent to which subsequence within a polypeptide comprising the amino acid sequence of SEQ ID NO: 1 the claims require the antibody to bind. For example, based upon the definition of "PSTPIP", the claims might reasonably be interpreted to encompass an antibody that binds to an amino acid sequence of a heterologous peptide, such as the FLAG epitope of a fusion protein also comprising the amino acid sequence of a protein having the ability to bind the specifically claimed protein tyrosine phosphatase and induce actin polymerization within a cell, but Applicants have argued that such antibodies are not regarded as the invention. Nonetheless, in view of the indefinite nature of the claims, one of ordinary skill in the art would not be reasonably apprised of the metes and bounds of the invention.

Claims 15-18 are vague and indefinite because claims 15 and 23 recite the term "rich". Recitation of the term "rich" in claims 15 and 23 renders the claims vague and indefinite because the term "rich" is a relative term, which is not defined by the claim. Since the specification does not provide a standard for ascertaining the requisite degree

of enrichment of the amino acids proline, serine, and threonine in the non-catalytic domain and proline in the C-terminal 20 amino acids of the protein tyrosine phosphatase to which PSTPIP must bind, which is required by the claims, one of ordinary skill in the art would not be reasonably apprised of the metes and bounds of the invention. Amending claims 15 and 23 to recite the particular degree of enrichment of the amino acids proline, serine, and threonine in the non-catalytic domain and proline in the C-terminal 20 amino acids of the protein tyrosine phosphatase to which PSTPIP must bind can obviate this rejection.

Claim 23 is vague and indefinite because the claim recites the phrase "contacting the PSTPIP polypeptide with a candidate antibody". Recitation of the phrase renders the claim vague and indefinite because it is not clear whether the claim requires the antibody to bind specifically to the PSTPIP polypeptide or merely to contact it. Accordingly, one of ordinary skill in the art would not be reasonably apprised of the metes and bounds of the invention.

Claim Rejections - 35 USC § 102

16. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

17. Claims 15-16 are rejected under 35 U.S.C. 102(b) as being anticipated by Sodhi, et al (*Biochemistry and Molecular Biology International* **35**: 559-565, 1995; see abstract).

Claims 15 and 16 are drawn to an antibody that binds specifically to a PSTPIP polypeptide sequence within a polypeptide, wherein the polypeptide comprises the amino acid sequence of the PSTPIP polypeptide that is set forth in SEQ ID NO: 1 (claim 15), wherein said antibody is detectably labeled (claim 16).

Sodhi, et al teach the use of anti-phosphotyrosine-FITC antibody, a fluorescently labeled and detectable antibody, to study proteins. It is an inherent property of the prior art antibody to specifically bind tyrosine-phosphorylated proteins. In light of the specification, it is clear that an anti-phosphotyrosine monoclonal antibody specifically binds to an amino acid sequence within the protein of SEQ ID NO: 1. Therefore, the prior art antibody clearly anticipates the claims since the antibody is known to bind specifically to a PSTPIP polypeptide sequence within a polypeptide comprising the amino acid sequence of SEQ ID NO: 1. Moreover, the prior art antibody clearly anticipates a detectably labeled antibody capable of specific binding to PSTPIP since, in light of the specification, fluorescein isothiocyanate (FITC) is preferably used as a detectable label.

All the limitations of the claims are met.

18. Claims 15 and 17-18 are rejected under 35 U.S.C. 102(b) as being anticipated by Frackleton, et al (*Journal of Biological Chemistry* **259**: 7909-7915, 1984; see abstract).

Claims 15 and 17-18 are drawn to an antibody that binds specifically to a PSTPIP polypeptide sequence within a polypeptide comprising the amino acid sequence of SEQ ID NO: 1 (claim 15) and a hybridoma cell line producing said antibody (claim 18), wherein the said antibody is a monoclonal antibody (claim 17).

Frackleton, et al teach the use of an anti-phosphotyrosine monoclonal antibody, which is produced by a hybridoma cell line, to isolate proteins. It is an inherent property of the prior art antibody to specifically bind tyrosine-phosphorylated proteins. In light of the specification, it is clear that an anti-phosphotyrosine monoclonal antibody specifically binds PSTPIP. Therefore, the prior art antibody clearly anticipates the claims since the antibody is known to bind specifically to a PSTPIP polypeptide sequence within a polypeptide comprising the amino acid sequence of SEQ ID NO: 1. In light of the specification and the art at the time of the invention, inherent in the production of a monoclonal antibody is the hybridoma cell line that produces a monoclonal antibody.

All the limitations of the claims are met.

Claim Rejections - 35 USC § 103

19. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

20. Claims 15-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Database GenBank Accession No. AI322422 (Marra, et al, 1996) in view of Ackerman (*Human Cell* **1**: 46-53, 1988).

Claims 15-18 are drawn to an antibody that binds specifically to a PSTPIP polypeptide sequence within a polypeptide comprising the amino acid sequence of SEQ ID NO: 1 (claim 15) and a hybridoma cell line producing said antibody (claim 18) wherein said antibody is detectably labeled (claim 16) or wherein the antibody is a monoclonal antibody (claim 17).

Database Genbank Accession No. AI322422 teaches the polynucleotide sequence of a mouse cDNA clone that encodes an amino acid sequence that is 98.2% identical to the region spanning amino acid residues 247 to 415 of SEQ ID NO: 1.

However, Genbank Accession No. AI322422 does not disclose antibodies that specifically bind to the protein encoded by the nucleic acid molecule; nor does it disclose specifically disclose monoclonal antibodies, hybridomas that produce antibodies, or detectably labeled antibodies.

Nevertheless, the prior art nucleic acid molecule would be expected to hybridize under the specifically claimed stringent conditions to the complement of residues 682 to 1926 of SEQ ID NO: 2. Accordingly, the nucleic acid molecule of the prior art is deemed the same as the nucleic acid molecule of the claims. Therefore, the antibodies that bind the protein encoded by the nucleic acid molecule of the prior art are deemed the same as the antibodies of the claims, absent a showing of unobvious differences.

Ackerman teaches that the hybridoma technology developed by Kohler and Milstein facilitated a revolution in biotechnology during which the possibility of generating monoclonal antibodies that specifically bind an antigen became routine in laboratories throughout the world. Because of the constant quality of the monoclonal antibody and the other numerous advantages that use of the monoclonal antibody provides, Ackerman teaches that monoclonal antibodies are used widely in many different applications and also finding use in many new and expansive applications.

Even though Database Genbank Accession No. AI322422 does not disclose antibodies that specifically the protein encoded by the nucleic acid molecule, which would be expected to hybridize under the specifically claimed stringent conditions to the complement of residues 682 to 1926 of SEQ ID NO: 2, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to make an monoclonal antibody that binds specifically to the protein encoded by the nucleic acid molecule of the prior art, because Ackerman demonstrates that the technology necessary to do so is conventional and routine and because the Board of Patent Appeals and Interferences has taken the position that once an antigen has been isolated, the manufacture of monoclonal antibodies against it is *prima facie* obvious. See *Ex parte Ehrlich*, 3 USPQ 2d 1011 (PTO BPAI, 1987) and *Ex parte Sugimoto*, 14 USPQ 2d 1312 (PTO BPAI, 1990). At the time the invention was made, the production and isolation of an antigen encoded by an isolated cDNA molecule was routine. It was also routine at the time the invention was made, to detectably label an antibody as a means for visually detecting the complex of the antigen to which the antibody binds and the antibody.

21. Claims 15-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Database GenBank Accession No. MMU87814 (Lasky, 29 January 1997) in view of Ackerman (*Human Cell* **1**: 46-53, 1988).

Claims 15-18 are drawn to an antibody that binds specifically to a PSTPIP polypeptide sequence within a polypeptide comprising the amino acid sequence of SEQ ID NO: 1 (claim 15) and a hybridoma cell line producing said antibody (claim 18)

wherein said antibody is detectably labeled (claim 16) or wherein the antibody is a monoclonal antibody (claim 17).

Database Genbank Accession No. MMU87814 teaches the polynucleotide sequence of a mouse cDNA clone that encodes an amino acid sequence that is identical to SEQ ID NO: 1.

However, Genbank Accession No. MMU87814 does not disclose antibodies that specifically bind to the protein encoded by the nucleic acid molecule; nor does it disclose specifically disclose monoclonal antibodies, hybridomas that produce antibodies, or detectably labeled antibodies.

Ackerman teaches that the hybridoma technology developed by Kohler and Milstein facilitated a revolution in biotechnology during which the possibility of generating monoclonal antibodies that specifically bind an antigen became routine in laboratories throughout the world. Because of the constant quality of the monoclonal antibody and the other numerous advantages that use of the monoclonal antibody provides, Ackerman teaches that monoclonal antibodies are used widely in many different applications and also finding use in many new and expansive applications.

Even though Database Genbank Accession No. MMU87814 does not disclose antibodies that specifically bind to the protein encoded by the nucleic acid molecule, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to make an monoclonal antibody that binds specifically to the protein encoded by the nucleic acid molecule of the prior art, because Ackerman demonstrates that the technology necessary to do so is conventional and routine and because the Board of Patent Appeals and Interferences has taken the position that once an antigen has been isolated, the manufacture of monoclonal antibodies against it is *prima facie* obvious. See *Ex parte Ehrlich*, 3 USPQ 2d 1011 (PTO BPAI, 1987) and *Ex parte Sugimoto*, 14 USPQ 2d 1312 (PTO BPAI, 1990). At the time the invention was made, the production and isolation of an antigen encoded by an isolated cDNA molecule was routine. It was also routine at the time the invention was made, to detectably label an antibody as a means for visually detecting the complex of the antigen to which the antibody binds and the antibody.

Response to Amendments and Remarks

22. In Paper Nos. 22 and 27 filed on July 9, 2001 and September 24, 2001, respectively, Applicants traverse the rejections made in the previous Office Action, which was mailed on March 21, 2001 (Paper No. 19).

Applicants argue that in part, the basis of the rejection of the claims under 35 USC § 112, first paragraph is contradictory to the view already taken by the Office, since the claims of issued US Patent No. 6,111,073-A are drawn to the same genus of PSTPIP molecules to which the claims in the instant application refer. While this argument is not necessarily found persuasive, it is noted that Applicants have amended claim 15 to recite the requirement that the PSTPIP molecule, which is encoded by a nucleic acid molecule that hybridizes under the stringent conditions to the complement of the fragment of SEQ ID NO: 2, have the ability to bind the protein tyrosine phosphatase and induce polymerization of actin monomers within a cell. While claim 15 does not recite the need that the PSTPIP molecule be over-expressed in the cell, it is again noted, as was stated in the previous Office Actions, that the specification does not demonstrate that the PSTPIP of SEQ ID NO: 1 is capable of stimulating actin polymerization in a cell under any circumstance other than the one in which the protein is over-expressed in the cell. Claim 23, on the other hand, makes clear the requirement that the candidate antibody have the ability to stimulate or inhibit the polymerization of actin monomers induced by over-expression of the PSTPIP molecule within the cell (lines 5-7). Therefore, in view of the disclosure and the limitations of claim 23, at least part of the grounds of rejection under 35 USC § 112, first paragraph, which were stated in the previous Office Action, are rendered moot by the amended language of the claims. However, despite acknowledging issue of US Patent No. 6,111,073-A, the Examiner maintains the contention that the disclosure is not enabling of the full breadth of scope of the claims since it is unclear from the disclosure whether most of the PSTPIP molecules encompassed by the claims of the instant invention can be used in accordance with the teachings of the specification or whether most will have either the

ability to bind the protein tyrosine phosphatase or the ability to induce actin polymerization within a cell when the PSTPIP is over-expressed in a cell.

Furthermore, Applicants state that without acquiescing to the Examiner's position, the language of the claim 23 has been modified relative to that of claim 22, which is now cancelled, to recite the requirement that the candidate agonist or antagonist antibody be "cell membrane permeable". If a candidate agonist or antagonist antibody were to be able to permeate the membrane of a cell to contact the PSTPIP within the cell, the integrity of the cell membrane would not need to be disrupted. However, due to the size of the molecules, antibodies are not naturally cell membrane permeable. Therefore, while inclusion of this limitation would indeed obviate at least part of the grounds of rejection under 35 USC § 112, first paragraph, which were set forth in the previous Office Action, it is noted that the disclosure fails to teach a method for producing an antibody that is able to permeate the membrane of a cell; see the 35 USC § 112, first paragraph rejection above. Applicants submit that the methods of conferring membrane permeability were well known in the art at the time the invention was made, as evidenced by the publications cited in Paper No. 16. However, as was pointed out previously in the response to this argument, none of the cited references teach a method for conferring cell membrane permeability to an antibody that specifically binds a PSTPIP molecule or for that matter, any other antibody. Furthermore, none of the cited references teach a method for conferring cell membrane permeability to a molecule that is otherwise impermeable to the cell membrane; instead it appears that each of the cited references teaches a method for adapting various active transport processes for shuttling modified molecules across the cell membrane, but none of the modified proteins are rendered permeable, *per se*. Thus, contrary to Applicants' assertion, there is no factual evidence suggesting that a method for conferring cell membrane permeability to an antibody that binds specifically to PSTPIP within a cell was well known in the art at the time the application was filed. To the extent of the Examiner's immediate knowledge, such a method is still not conventionally known in the art.

Nevertheless, Applicants state that claim 15 has been amended and claim 23 has been added and that both claims now recite the requirement that the PSTPIP encoded by the nucleic acid molecule that hybridizes under the stringent conditions to the complement of a fragment of SEQ ID NO: 2 retain both the ability to bind the protein tyrosine phosphatase and the ability to induce polymerization of actin monomers within a cell. The inclusion of the dual requirement obviates at least part of the grounds of rejection of the claims, which were stated in the previous Office Actions, namely as containing subject matter that is not adequately described in the disclosure to meet the requirements of 35 USC § 112, first paragraph. The currently pending claims do not encompass antibodies that bind to PSTPIP molecules encoded by a nucleic acid molecule that hybridizes under the stringent conditions to the complement of the fragment of SEQ ID NO: 2, which do not have the ability to bind the protein tyrosine phosphatase and induce actin polymerization within the cell. However, as discussed in the rejection above, the written description is still inadequate to meet the requirements of 35 USC § 112, first paragraph.

Applicants argue that the recitation of specific wash conditions in claims 15 and 23 is unnecessary since "while some experimentation may be necessary to reduce the background to the desired level, this does not constitute undue experimentation" (page 7, paragraph 4). Certainly one skilled in the art would be expected to be able to determine the optimal conditions of the wash, i.e., the duration and frequency of the wash(es), that would be necessary to practice the claimed invention without undue experimentation; therefore, with regard to this particular basis of rejection, Applicants' arguments are found persuasive. Even so, it is again noted that the wash conditions, which are recited in the claims, are only stringent wash conditions, according to the teachings of the specification. Because it would seem that highly stringent wash conditions would be preferable since the increased stringency of the condition could be expected to reduce the number of nucleic acid molecules that hybridize to the complement of the fragment of SEQ ID NO: 2, which might encode proteins that do not fulfill the functional requirements of the claims. Therefore, it is not evident that Applicants have set forth specifically claimed the best mode for practicing the invention.

Finally, Applicants argue that the amendment to the claims obviates the basis of the rejection of the claims under 35 USC §§ 102 and 103; however, these arguments are not found entirely persuasive. For example, clearly the amendments to claim 15 do not serve to distinguish the claimed antibody from some of the antibodies of the prior art. With regard to Applicants' argument (Paper No. 22, paragraph bridging pages 8 and 9), it is appropriately noted that a monoclonal antibody, namely the anti-phosphotyrosine antibody of the prior art does, in fact, bind specifically to the polypeptide of the claim. Furthermore, the inclusion of the phrase "sequence within a polypeptide" in claim 15 by the amendment of Paper No. 27 also does not distinguish the subject matter of the claim from the prior art, since the antibodies of Sodhi, et al and Frackelton, et al have been demonstrated to bind specifically to a PSTPIP polypeptide sequence within a polypeptide comprising the amino acid sequence of the PSTPIP polypeptide of SEQ ID NO: 1. For this reason, the rejections of claims 15-18 under 35 USC § 102(b) as being unpatentable over the teachings of Sodhi, et al or Frackelton, et al are reiterated herein.

On the other hand, if one overlooks the incongruity of the disclosed definition of "PSTPIP" in the specification, which was discussed above, the inclusion of the phrase "sequence within a polypeptide" in claim 15 would serve to distinguish the subject matter of the claim from the prior art antibody of Su, et al. In such a case, the currently pending claims are restricted to antibodies that bind specifically to an amino acid sequence contained within the amino acid sequence set forth in SEQ ID NO: 1. Accordingly, it is fairly obvious that the antibodies of Su, et al do not bind specifically to a PSTPIP polypeptide sequence (i.e., a portion of SEQ ID NO: 1) within a polypeptide comprising said sequence. The antibodies of Su, et al bind specifically to the amino acid sequence of the FLAG epitope within the fusion protein comprising the amino acid sequence of SEQ ID NO: 1 and the amino acid sequence of the FLAG epitope. Giving Applicants the benefit of having overlooked the definition of "PSTPIP", the rejection of the claims under 35 USC § 102(b) as being anticipated by Su, et al is withdrawn.

Since the nucleic acid molecule of SEQ ID NO: 2 will hybridize under the specifically claimed conditions to the complement of nucleic acid residues 682 to 1926

of SEQ ID NO: 2, the inclusion of the phrase "residues 682 to 1926" in claims 15 and 23 does not serve to distinguish the claimed subject matter from the prior art antibodies of Parthun, et al, but the subject matter of the claims would be distinguished from the antibodies of Parthun, et al, again if the incongruity of the definition of "PSTPIP" is overlooked, because it is fairly obvious that the antibodies of Parthun, et al will not bind specifically to a "PST phosphatase interacting protein (PSTPIP) polypeptide sequence" (i.e., a portion of SEQ ID NO: 1) within a polypeptide encoded by a nucleic acid molecule that hybridizes under the stringent conditions to the complement of the fragment of SEQ ID NO: 2. As stated in the previous Office Action, the antibodies of Parthun, et al bind specifically to an amino acid sequence of the GAL4 activation domain within the protein encoded by SEQ ID NO: 2, which appears to comprise both the amino acid sequence of SEQ ID NO: 1 and the amino acid sequence of the GAL4 activation domain. Consequently, again giving Applicants the benefit of having overlooked the definition of "PSTPIP", the rejection of the claims under 35 USC § 102(b) as being anticipated by Parthun, et al is withdrawn. Nonetheless, for the reason set forth above, recitation of the phrase "a PST phosphatase interacting protein (PSTPIP) polypeptide sequence within a polypeptide" in claim 15 is considered to render the claim vague and indefinite and therefore the claim fails to meet the requirements of 35 USC § 112, second paragraph. Furthermore, such a limitation recited in the present claims, introduces new concepts and violates the written description requirement of 35 USC § 112, first paragraph, because the language of the limitation does not appear to be explicitly or implicitly supported by the disclosure in the originally filed specification.

For the reason discussed in the paragraph above, the rejections under 35 USC § 103(a), which were made in the previous Office Actions, are withdrawn.

Conclusion

23. No claims are allowed.

24. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen L. Rawlings, Ph.D. whose telephone number is

(703) 305-3008. The examiner can normally be reached on Monday-Thursday, alternate Fridays, 8:00AM-5:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony C. Caputa, Ph.D. can be reached on (703) 308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Stephen L. Rawlings, Ph.D.
Examiner, Art Unit 1642

DONNA WORTMAN
PRIMARY EXAMINER

slr
November 18, 2001